REMARKS

Status of the Claims

Claims 36-51 are pending in this application.

Claims 36-51 stand rejected.

Claim Rejections

35 U.S.C. § 112, ¶1

The Examiner has rejected claims 36-51 under §112, first paragraph, as lacking enablement. Briefly, the Examiner contends that the data in Applicants' specification demonstrating that perilla oil prevents the upregulation of PPAR is insufficient to satisfy the enablement requirement because, according to the Examiner, "there is no nexus between cellulite and the prevention of upregulation of PPAR." During an October 12, 2005 interview, the Examiner indicated that "[c]ompetent documentation establishing this nexus would be given careful consideration." (Interview Summary). Applicants provide herewith such documentation for the Examiner's consideration and respectfully request reconsideration of this rejection based on the following remarks.

The Examiner relies on the statement in the Van Villet abstract that "there is no consensus as to the etiology of cellulite" to support the contention that Applicants' data showing prevention of PPAR upregulation does not enable claims to methods of "ameliorating or treating cellulite." Applicants submit that a single abstract does not reflect whether there is a consensus in the art, and furthermore whether or not there is "consensus" as to the etiology of cellulite is irrelevant. The etiology of many diseases and conditions is unknown, although certain biological pathways, enzymes, gene expressions, etc. may form the basis for developing treatments even if they are unrelated to the specific causative basis of the condition or disease. Indeed, in the case of cellulite, there is considerable evidence as to the central role of PPAR.

A. The USPTO Has Issued A Patent For A Topical Oil Which Reduces PPAR mRNA Expression For The Treatment Of Cellulite

In fact, the USPTO has granted U.S. Pat. No. 6,852,343 ("the '343 patent") with claims directed to the treatment of cellulite using compounds said to reduce PPARγ2 mRNA expression. The anticellulite compounds of the '343 patent are oils extracted from *Allium sativum* (garlic) bulbs. The oils are termed "EO" (essential oil) or ACH, ACEA, and AOA

depending on the extraction solvent (viz., hexane, ethyl acetate, and acetone, respectively). [col. 8, lines 32-45].

The '343 patent explicitly makes the connection between the PPAR signaling pathway and cellulite treatment. The '343 patent discloses that the etiology of cellulite involves the differentiation of preadipocytes into mature adipocytes, which are capable of accumulating triglycerides [col. 2, lines 24-44] and suggests that inhibition of the conversion of the preadipocytes into mature adipocytes "offer[s] a novel and interesting approach in the treatment of cellulite" [col. 2, lines 45-51].

Example 3 of the '343 patent, titled "Effect of the EO, ACH, ACEA or AOA Solutions on the Expression of PPARγ2 mRNA," provides data showing that the "level of expression of the PPARγ2 adipogenic transcription factor is greatly reduced when 3T3-F442 cells have been in contact with" the anticellulite EO, ACH, ACEA and AOA solutions. Example 3 of the '343 patent states that "[a]dipocyte differentiation is an important feature of the development of adipose tissue and obesity" and that the "adipocyte differentiation process is characterized in vitro by the programmed induction of various genes regulating lipoprotein lipolysis, fatty acid capture by cells, and fatty acid and triglyceride synthesis." [col. 11, lines 24-29]. The patent states that expression of PPARγ2 mRNA is an early marker of differentiation [col. 11, lines 29-32] such that the "degree of differentiation of the adipocyte can thus be established by studying the level of expression of the appropriate markers like PPARγ2 mRNA . . ." [col. 11, lines 43-46].

Moreover, PPAR is clearly stated to be implicated in the etiology of, rather than simply an associated marker for, cellulite. For example, the '343 patent states that "[w]hen PPARγ2 is activated, it induces the transcription of several adipocyte genes encoding proteins and enzymes involved in the creation and maintenance of the adipocyte phenotype" and "thus, plays a fundamental role in the differentiation and metabolism of adipose cells" [col. 11, lines 56-61]. Example 3 concludes that the oil extracts "act on the differentiation program by reducing the expression of the PPAR γ2 messenger." [col. 12, line 65-col. 13, line 5]. This is a clear teaching of a connection between inhibition of upregulation of PPAR and cellulite treatment.

B. There Are Numerous Studies Demonstrating Efficacy of Therapeutic Agents For Treating Cellulite

The Examiner relies on the statement from the Avram abstract ("Cellulite: a review of its physiology and treatment," J. Cosmetic & Laser Therapy, (2004) Vol. 6, Issue 4 pp.181-185) that "[t]here are no truly effective treatments for cellulite," to support the contention that the present claims lack enablement. Applicants submit that the Examiner has placed undue reliance on this statement because: (1) the term "effective" is modified by the relative term "truly," which does not negate some degree of efficacy; and (2) several anti-cellulite therapeutics have clinically demonstrable efficacy, as discussed below.

The Examiner's attention is drawn to the article Lawrence Birnbaum, M.D., "Addition of Conjugated Linoleic Acid to a Herbal Anticellulite Pill," *Adv. Ther.* (2001) Vol. 18, No. 5, pp. 225-229, submitted herewith. This paper reports the results of a 60 day study on the efficacy of daily oral administration of conjugated linoleic acid (CLA) in combination with a commercially available herbal anticellulite pill on visible cellulite in the thigh. Sixty female subjects were divided into three groups: Group 1 received the herbal anticellulite pill alone; Group 2 received the herbal anticellulite pill plus 400 mg of CLA; and Group 3 received the herbal anticellulite pill plus 800 mg of CLA. At the end of the 60 day treatment regimen, the women in Group 3 had an average reduction in thigh circumference of 0.88 inches, compared to a reduction of 0.58 inches for Group 2 and 0.33 inches for Group 1. Further, 75% of the women in Group 3 showed improvement in thigh cellulite at the end of the study, as compared to 44% in Group 2 and 15.4% in Group 1. The authors conclude that while the "anticellulite pill had a minor positive effect on the appearance of cellulite in a small number of patients . . . [t]he addition of CLA, however, dramatically improved all the indices evaluated." [p. 228]. Clearly, this report documents "effective" cellulite treatment.

Further, a paper by Bertin et al., "A double-blind evaluation of the activity of an anti-cellulite product containing retinol, caffeine, and ruscogenine by a combination of several non-invasive methods," *J. Cosmet. Sci.* (2001) vol. 52, pp. 199-210, submitted herewith, reports the results of a three-month randomized, double-blind, placebo-controlled study that tested the effects of a topical product containing retinol, caffeine, and ruscogenine on various measures of cellulite in the thighs of 46 women with moderate levels of cellulite. Subjects applied the indicated anti-cellulite treatment to one thigh twice daily for three months and applied a placebo treatment to their other thigh twice a day for three months. The various end-points were

measured before the first application, and then after 28 days, 56 days, and 84 days of application, and included macrorelief of the skin (digital imaging assessment of the "orange peel" effect), structure of the dermis and hypodermis via 3D ultrasound imaging, mechanical characteristics of the skin (cutometry, to assess parameters such as skin elasticity, extensibility, deformation, recovery), and flowmetry of skin perfusion to assess skin microcirculation. By day 84, the anti-cellulite topical product had significantly reduced the "orange peel" appearance of treated skin compared with placebo (53.0% versus 14.1% reduction), and by day 28, there was a significant increase in mean blood flow in treated thighs as compared to the placebo treatment, indicating improved microcirculation. The authors conclude that the product tested was "significantly active on the 'orange peel' appearance of the skin, which is the most apparent manifestation of cellulite..." [p. 209]. Bertin demonstrates thus another example of an effective treatment.

Similarly, Rao et al., "A two-center, double-blinded, randomized trial testing the tolerability and efficacy of a novel therapeutic agent for cellulite reduction," *J. Cosmet. Dermatol.* (2005) **4**, 93-102, submitted herewith, details the results of placebo controlled, double blind study of the efficacy of an anticellulite cream. The cream comprised the seven ingredients listed in Table 5 (p. 101) which were suggested to have vasodilation and lypolysis activity. The cream was applied daily for four weeks to either the right or left thigh of 40 women and to the contralateral thigh was applied a placebo control. Five blinded, independent physician reviewers assessed high-quality digital photographs taken before treatment and after four weeks of treatment and found that the treated thighs showed greater improvement than thighs treated with placebo in 68% of subjects. Patient self-evaluation was in good agreement, with 62% of subjects reporting greater improvement in the treated thigh. The authors conclude that the "study demonstrates that a topical agent based on current mechanistic knowledge of cellulite formation can be used to treat this unwanted condition" (p. 101) and that the "active topical agent used in this study was found to be effective in reducing the appearance of cellulite." (p. 93).

Clearly, the foregoing studies demonstrate that clinically effective treatments for cellulite are known in the art. Avram's statement that "[t]here are no truly effective treatments for cellulite" is a statement in a single abstract. As Applicants document herein, both the USPTO and the peer-reviewed scientific literature recognize that effective therapies for cellulite exist as well as a nexus between cellulite and PPAR. Accordingly, the Examiner's reliance on Avram is misplaced and Applicants respectfully request withdrawal of this ground of rejection.

C. The '343 Patent Provides Evidentiary Support For The Conclusions Set Forth In The Declaration of Dr. Elias

The Declaration of Dr. Elias is fully consistent with the teachings of the '343 patent, discussed above, and provides further support for the fact that PPAR is understood by those of skill in the art to be implicated in the etiology of cellulite. Dr. Elias explains that "PPARgamma receptors regulate adipocyte growth and differentiation" and therefore it "follows that blocking PPARgamma receptors would be a suitable means for treating or ameliorating cellulite." Dr. Elias is an expert in skin biology and dermatology and has authored over 30 publications focusing on the effects of PPAR activators in skin biology. Applicants submit that the Examiner has afforded insufficient weight to Dr. Elias' conclusions, dismissing the declaration as "opinion." Applicants remind the Examiner that a "declaration or affidavit is, itself, evidence that must be considered." MPEP § 2164.05. Thus, the declaration must be considered as evidence tending to show that those of skill in the art recognize that PPAR represents a rational target for treating cellulite, particularly in view of the factual evidence provided above, also supporting this conclusion.

In sum, Applicants submit that the knowledge in the art, as evidenced by the '343 patent and the declaration of Dr. Elias, is sufficient to establish PPAR as playing a central role in the etiology of cellulite. In this regard, Applicants point out that the "evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art." MPEP §2164.05. The declaration of Dr. Elias is evidence that the disclosure of the present application is convincing to one skilled in the art that inhibition of upregulation of PPAR would be an effective treatment for cellulite.

The Examiner refers to Dr. Elias' statement that he is "not aware that PPARgamma stabilizers have been employed to treat cellulite in the skin biology or dermatology art outside of the disclosure" of the present application to support the contention that preventing the upregulation of PPAR does not enable the treatment of cellulite. That Dr. Elias might not have been aware of all the literature in this broad field does not negate his scientific conclusion that "blocking PPARgamma receptors would be a suitable means for treating or ameliorating cellulite." Indeed, inhibiting upregulation of PPAR is a known approach for treating cellulite as evidenced by the '343 patent, discussed above.

CONCLUSION

Applicants respectfully submit that the instant application is in condition for allowance. Entry of the amendments and an action passing this case to issue is therefore respectfully requested. In the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided.

Respectfully submitted,

Dated: May 31, 2007

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Addition of Conjugated Linoleic Acid to a Herbal Anticellulite Pill

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ABSTRACT

This study investigated the effect of a herbal anticellulite pill on visible cellulite in the thighs. Sixty female volunteers took a herbal anticellulite pill or a herbal anticellulite pill plus supplements of conjugated linoleic acid for 60 days. The combination treatment had a beneficial effect in as many as 75% of the women. The appearance of the skin improved significantly, and thigh circumference was reduced by an average of 0.88 inch. Further investigation in a larger, longer placebo-controlled trial is warranted.

Keywords: conjugated linoleic acid; cellulite; thermography

INTRODUCTION

Surgical procedures designed to improve the appearance of cellulite have all demonstrated limited success. They consist primarily of undermining the involved skin area in an attempt to disrupt the fibrous septa that create the characteristic dimpling. Recent interest has centered on use of an external suction roller device, which, though effective in many patients, is time-consuming and costly and requires ongoing maintenance. Similar improvements have occurred with ultrasonography, vigorous brushing of the involved areas, and topical application of creams. These interventions are also expensive and time-consuming. Reports of a herbal anticellulite pill surfaced in the media in 1998, but copies of the alleged studies supporting the pill's efficacy have remained elusive.

This pilot study was initiated to (1) document improvements in cellulite with the herbal anticellulite pill and (2) ascertain whether the addition of conjugated linoleic acid (CLA) might yield further benefit. Considerable evidence demonstrates the benefits of CLA in reducing fat and altering

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body dimensions.[1-5] The resultant lean body mass may conceivably improve the appearance of cellulite simultaneously.

MATERIALS AND METHODS

Sixty female volunteers with visible cellulite on the thigh were recruited into the study. Their average age was 40 years (range, 26–55 years), and average weight was 136 lbs (range, 120–201 lbs).

The women were placed into three randomly chosen groups of 20. Each day for 60 days, Group 1 took the herbal anticellulite pill alone; Group 2 took the herbal anticellulite pill plus 400 mg of CLA; and Group 3 took the herbal anticellulite pill plus 800 mg of CLA.

The pills were formulated with the same ingredients present in a well-known marketed brand. CLA was provided in a gelatin shell capsule (shell 100 mg, CLA 400 mg per capsule) and was conjugated to 80% to ensure the highest possible percentage of active isomers.

Participants were instructed not to change their dietary or exercise habits and to continue current medications or dietary supplements for the duration of the study. No medications or supplements could be added without notification of the investigators. Each participant was monitored at 2-week intervals. At these visits, compliance with the study protocol was ascertained; the women were weighed; and waist and mid-thigh circumferences were measured. In addition, changes in cellulite were evaluated on the basis of the following four criteria:

1. Standardized photographs were taken with a 35-mm photo station designed to record the appearance and severity of the cellulite. The equipment ensured that camera position and angle, lighting, and distance from and positioning of the subject remained constant. Consequently, accurate photographic evidence was guaranteed, and skin condition before and after treatment was properly recorded and assessed.
2. Each participant was placed in a temperature-controlled room for at least 10 minutes to equilibrate body temperature, after which thermographic scanner plates were applied to fixed areas on the thighs. The microencapsulated liquid crystals in these scanners accurately monitor surface temperature by registering different colors to produce a thermal map. Thus, the microcirculatory condition of fat cells beneath the skin can be determined. The resultant images were photographed with a mounted, fixed Polaroid camera that ensured constant position and distance from the subject, camera angle, and lighting. The photographs were graded for severity of cellulite according to the criteria of Curri[6,7] in studies of the microcirculatory patterns of cellulite.
3. On the basis of these images, the investigators graded each subject's degree of cellulite as 1 = barely visible; 2 = readily visible but minimal; 3 = moderate; or 4 = severe.
4. Participants used the same scale to self-rate their cellulite.

RESULTS

Of the 60 women initially enrolled, 43 completed the entire 60-day study. Noncompleters were not included in the results. The primary reason for premature

withdrawal was failure to make scheduled visits. One participant each in Groups 1 and 2 dropped out because of perceived intolerance to the pills manifested as nausea.

Results were based on 13 completers in Group 1, 18 in Group 2, and 12 in Group 3. It had been decided to regard as a positive outcome only those improvements in all study parameters (ie, investigator observations combined with photographic documentation and subject self-assessment). Improvement was rated as none noted, minimal, moderate, or marked.

Group 1

Standardized thigh circumference measurements recorded an average loss of 0.33 inch (Fig 1). Two women had visible but minimal improvement in the appearance of cellulite; 11 showed no improvement (Fig 2).

Group 2

Thigh circumference decreased an average of 0.58 inch (Fig 1). Eight women showed improvement in cellulite: visible but minimal in five, marked in two, and moderate in one woman. Ten members of this group did not improve (Fig 2).

Group 3

Thigh circumference showed an average loss of 0.88 inch (Fig 1). Of the nine women whose cellulite improved, two had visible but minimal improvement; five displayed moderate improvement; and two showed marked improvement. No improvement was noted in three women (Fig 2).

Fig 1. Standardized thigh circumference measurements at end of study.

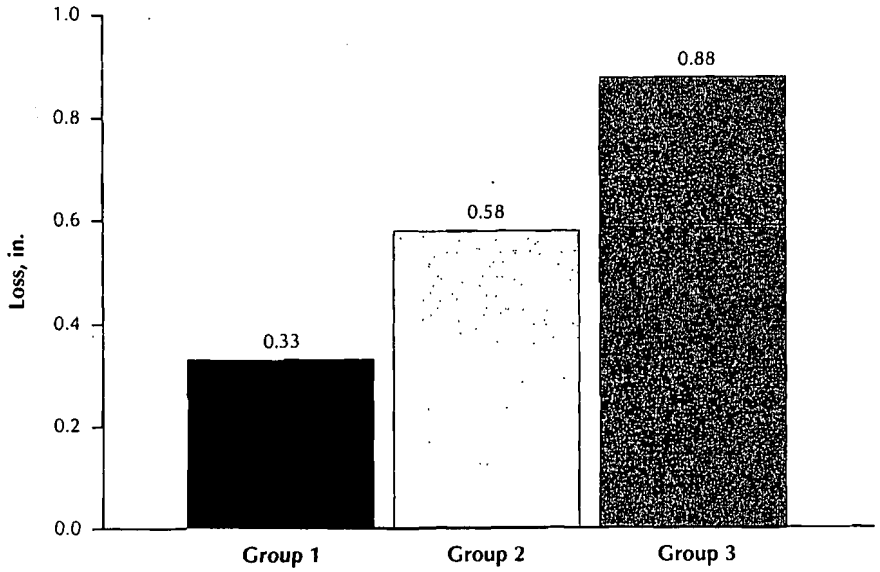
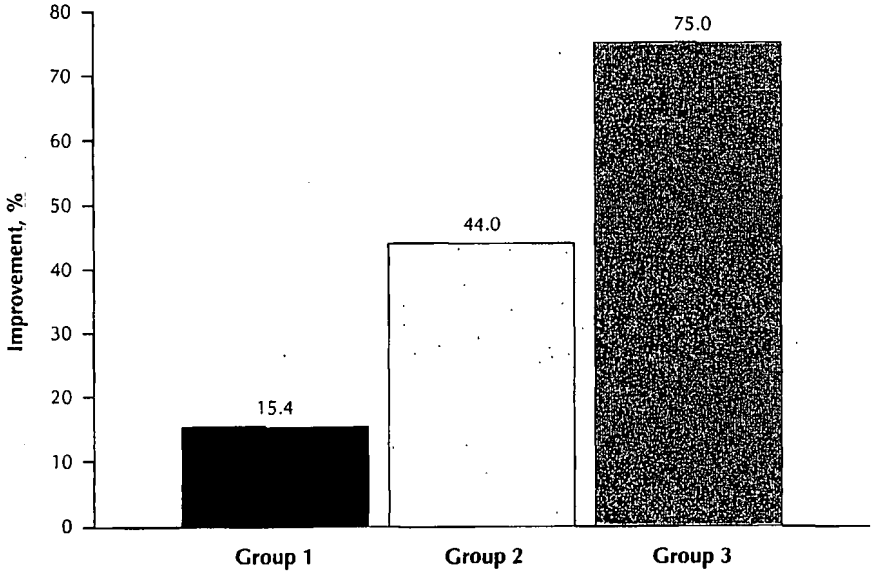


Fig 2. Percentage of women showing improvement in thigh cellulite at end of study.



DISCUSSION

In this study, a herbal anticellulite pill had a minor positive effect on the appearance of cellulite in a small number of patients. The addition of CLA, however, dramatically improved all the indices evaluated. The diminution in thigh measurements is in line with that observed in other studies of CLA and appears to validate them.

The thermographic results in our study are more difficult to interpret. They seem to indicate an improvement in the microcirculatory patterns in each group, although, clearly, the outcomes were more dramatic in the women who received supplemental CLA. If cellulite were to improve, the microcirculatory patterns would be expected to benefit as well. It is unclear from the studies of Curri[6,7] whether the microcirculatory patterns noted in the various stages of cellulite in some way caused the condition or were merely a result thereof. If any causative effect were operative, perhaps the thermographic improvements in women without *visible* improvement in the present study could be precursors of future benefits that might result from administration of the anticellulite agents for a longer time.

CONCLUSIONS

When this study to test the validity of claims made for an anticellulite herbal pill was designed, it seemed worthwhile to include groups that examined the effects of adding CLA. Although minor improvements in the appearance of cellulite occurred in some women who took the herbal pill alone, the results obtained with the CLA

supplement were more impressive and occurred in a higher percentage of participants. Further investigation in a longer, larger trial that includes a placebo control group is warranted.

ACKNOWLEDGMENT

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J. Cosmet. Sci., 52, 199–210 (July/August 2001)

A double-blind evaluation of the activity of an anti-cellulite product containing retinol, caffeine, and ruscogenine by a combination of several non-invasive methods

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Synopsis

A double-blind, randomized, placebo-controlled study was conducted with 46 healthy female volunteers in order to test an anti-cellulite product containing retinol, caffeine and ruscogenine. An evaluation of different parameters related to cellulite appearance, i.e., the skin macrorelief, the dermal and hypodermal structures, the skin mechanical characteristics, and the cutaneous flowmetry was assessed using several non-invasive methods.

This combination of different evaluation methods resulted in the demonstration of significant activity of the anti-cellulite product versus baseline and showed its superiority versus the placebo in skin macrorelief (decrease of the "orange peel" effect) and an increase in cutaneous microcirculation. By using a combination of methods, it was possible to detail the activity of an anti-cellulite product and to show superiority of the product in comparison with the placebo.

INTRODUCTION

Even though the subject of cellulite has received only minimal attention from the medical and scientific communities, it is nevertheless a real skin condition from which a high proportion of the female population actually suffers (1). This skin condition is associated with dimpling of the skin, or so-called "orange-peel" skin on the thighs and buttocks, and results from modifications of fat and fibrous tissue underlying the skin.

Although the sequence of events leading to the appearance of cellulite is still debated, the cellulite-prone appearance results from the combination of fat lobule enlargement with reactive focal fibrosclerotic hyperplasia of connective tissue strands, composed primarily of collagen and elastin fibers, partitioning the subcutaneous tissue.

Lymphatic and venous circulation in the tissue are impaired, and exchanges between the blood, the lymph, and the tissues are decreased (2,3). This may contribute to the damage of the fibroelastic strands. A vicious cycle ensues, in which enlarged fat lobules increase the hypodermal pressure, further damaging the vessels and degrading the fibers (collagen and elastin fibers). Fat lobules are squeezed upward upon pinching the skin, while their belt of fibrosclerotic strands acts like shrouds bound to the deepest fascia (4).

The skin on the thigh in women is easily deformed because the dermis is thin and the collagen bundles and the elastic network are vertically oriented, leading to the "orange peel" effect when the fibers are damaged. As the condition worsens, the dimpled aspect of the skin occurs spontaneously, without even pinching the skin.

This study evaluated the effect of the association of three active ingredients present in a cosmetic product: caffeine, ruscogenine extract, and retinol. The evaluation of the test product was performed using an original combination of objective methods, which had not yet been used:

- Profilometric analysis of the skin's macrorelief of the external face of the thighs performed on digital images of pinched thighs
- 3D ultrasound imaging (evaluation of the dermal and hypodermal structures)
- Cutometry (evaluation of the mechanical properties of the skin of the thighs)
- Laser Doppler flowmetry (evaluation of the cutaneous microcirculation)

MATERIAL AND METHODS

PANELISTS

Forty-six (46) healthy female volunteers, minimum 18 years of age, with normal skin were selected. They presented with a moderate level of cellulite in the thighs, and their weight/height ratio [body mass index (BMI) = weight/height] was between 20 and 25. All volunteers gave their informed written consent before beginning the test.

STUDY DESIGN

The format was a randomized, double-blind, placebo-controlled study. The study lasted three months (from the beginning of March until the end of May, 1999), the products were applied twice a day for three months (one thigh treated with the product and the other with the placebo). Measurements were taken before the first application, and then after 28 days, 56 days, and 84 days of application.

PRODUCTS

The complete product contained retinol, caffeine, ruscogenine extract, and alcohol. The placebo did not contain retinol, caffeine and ruscogenine extract (the alcohol was maintained to give the same cosmetic perception on application).

APPLICATION OF PRODUCTS

The volunteers applied both products regularly and uniformly over the entire thigh by circular massage. Products were applied twice daily, under in-use conditions.

POSITIONING OF SITES

Measuring sites on the thigh were marked with indelible ink after visual positioning at the summit of the cellulite bulge on the exterior lateral aspect of the thigh, at the same height from the ground for each thigh.

EVALUATION OF EFFECTIVENESS

Effectiveness was evaluated by the measurement of different parameters and their evolution:

- Macro-relief of the skin ("orange peel" effect)
- Structure of the dermis and hypodermis
- Mechanical characteristics of the skin
- Flowmetry of the skin perfusion

The following measuring devices were used:

1. Macrorelief of the skin: Profilometry on digital imaging of pinched thighs

The technique consists of acquiring macroscopic photographs of an area on the external lateral aspect of the thighs (5). In order to accentuate the unevenness of the skin's surface caused by cellulite, a localized controlled pinching was applied to the thigh using a compression system under standardized conditions (for each volunteer, the same pressure was applied throughout the study, around 200 g/cm^2). An incident lighting system was used to accentuate the relief and the skin dimple. All images were acquired with a CCD-RGB type XC-711/711P camera (Sony) equipped with a 60-mm focal length lens (Nikon). Digital images were analyzed using a dedicated software package (Visilog 5.00–NOESIS). Image analysis consisted of measuring the macrorelief of the skin surface. The zone under study corresponded to 15 jointive profiles (1 pixel width × 650 pixels length) corresponding to a skin surface area of 390 mm^2. The conventional Rz roughness parameter frequently used to describe cutaneous relief was used. In our case, this parameter was estimated from the slope a_i between two contiguous pixels (calculated from gray-level values).

2. Structure of the dermis and hypodermis: 3D ultrasound imaging

Significant parameters quantifying cellulite had been determined during a previous study (6).

Sonograph. The imaging equipment used was a sonograph from Esaote Company (AU4-AU5 model) provided with a high-frequency 20-MHz probe with low penetration (19-mm maximum) intended for the imagery of the skin, in particular of dermis and hypodermis.

Acquisition system and data processing. The images delivered by the sonograph were taken on the external lateral surface of the thighs via the video exit of the apparatus by a dedicated workstation (Iô 3.3, IôDP, Paris, France).

Three-dimensional sensor. The sonograph delivered an image in real time of the studied area. The probe was then moved in a predefined motion, allowing a digitalized sequence of images representative of the area covered to be generated.

Thus, to analyze the parameters of cellulite, it was preferable to acquire sequences of

images representing the zones to be quantified locally in order to multiply information describing the skin. Moreover, a three-dimensional positioning sensor was placed on the sonograph probe in order to be able to associate the images delivered by the sonograph with their positions and their orientation in space. Open3D® technology from IôDP was used. The region of interest (the scanning area) depends on the width of the probe (15 mm) and the motion of the probe during acquisition. We moved the probe for about 20 mm for each acquisition to get a scanned area of 15 mm × 20 mm. Parameters measured were dermal thickness, dermal echogenicity, dermal texture, hypodermal echogenicity, hypodermal texture, hypodermis cellulite ratio, and dermal hypodermal interface.

Dermal thickness. The value of dermal thickness is the average of the distances measured between the higher contour that materializes the limit of the skin and the lower contour that defines the limit between dermis and hypodermis. The calibration that makes it possible to establish the connection between the pixels of the image and the millimeter is carried out with the assistance of the sonograph: 234 pixels corresponding to 10 mm. Figures 1 and 2 show the results obtained for a sample.

Dermal and hypodermal echogenicity. In the average image (Figure 1B), the dermis is perfectly identified as being the zone delimited by contours red (a) and blue (b). The value of dermal echogenicity is the average of the values of echogenicity of this area. The hypodermal echogenicity is calculated, in the same way, for the area registered between contours blue (b) and green (c).

Dermal and hypodermal texture. Textures of an image can be regarded as particular arrangements of items or elementary groupings of items. We conceive this kind of texture as an organized area of pixels. The acoustic signal that builds up the images produces special organized patterns that show similar organization when the region of the body presents a homogeneous structure. These groupings of elementary items present a certain degree of similarity, making it possible to define, for a given texture, a concept of homogeneous area. Thus, the relations of dependence can characterize a texture, which exists between the gray levels of the points of its image.

In our case, texture is a parameter describing the capacity of an item for the image to be repeated in the image balanced by the difference of the gray levels that constitute it. Thus, a low value of texture comes from a low contrasted zone without items. On the contrary, a value for high texture expresses items that are repeated with strongly different values of echogenicity. The values of texture are calculated for each image in the zones defined by the dermal and the hypodermal contours.

Hypodermal cellulite ratio. The ratio of cellulite in the hypodermis is calculated in the original sequence as the ratio of the number of pixels of weak echogenicity, typical of the echogenicity of fat, over the total number of pixels in the hypodermis.

Dermal–hypodermal interface. The variations of the interface between dermis and hypodermis are underlined by the assistance of the three-dimensional rebuilding function of the Iô 3.3 station. An automatic thresholding based on the maximization of the variance is carried out in order to separate dermis from hypodermis as well as possible. This treatment is necessary in order to exclude the possibility of subjective interpretation to separate dermis from hypodermis. The relationship between the developed surface described by the border between dermis and hypodermis on the analyzed skin surface provides a parameter translating the undulations of the junction between dermis and hypodermis.

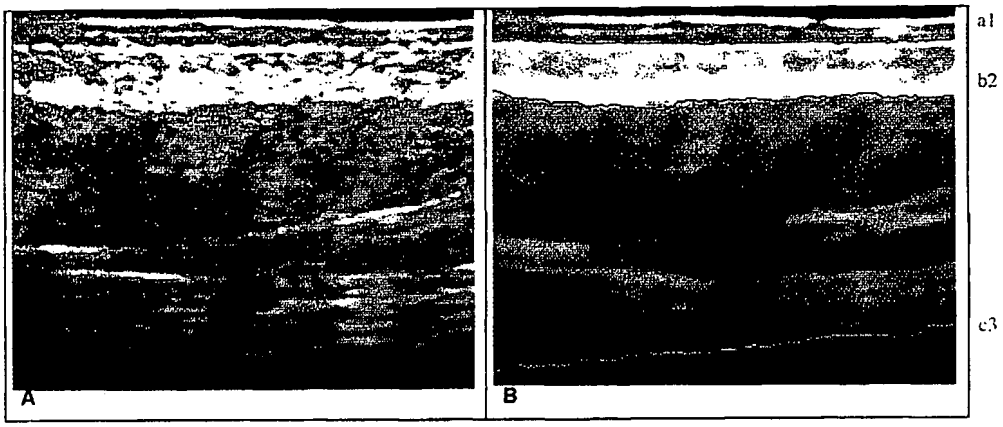

Figure 1. Visualization by sonograph of the three layers of the skin. (A) Skin slice by B-mode sonography with a 20-MHz probe. (B) Computed image from grabbed images and contours.

3. Mechanical characteristics of the skin: Cutometry

Measurements (three measurements on each thigh) were performed with the SEM 575® cutometer (Courage & Khazaka) on the external part of the thigh (7). The measurements were conducted in an air-conditioned room (22+/-2°C, HR 50+/-10%) after 20 minutes of rest period.

The time-strain mode was used with an elementary load cycle consisting of an instantaneous deformation by a 500-mbar negative pressure, maintained for three seconds and followed by a three-second relaxation period, with a probe of 6-mm diameter. Three repetitions of this cycle were performed. Suction was applied with a 6-mm diameter probe.

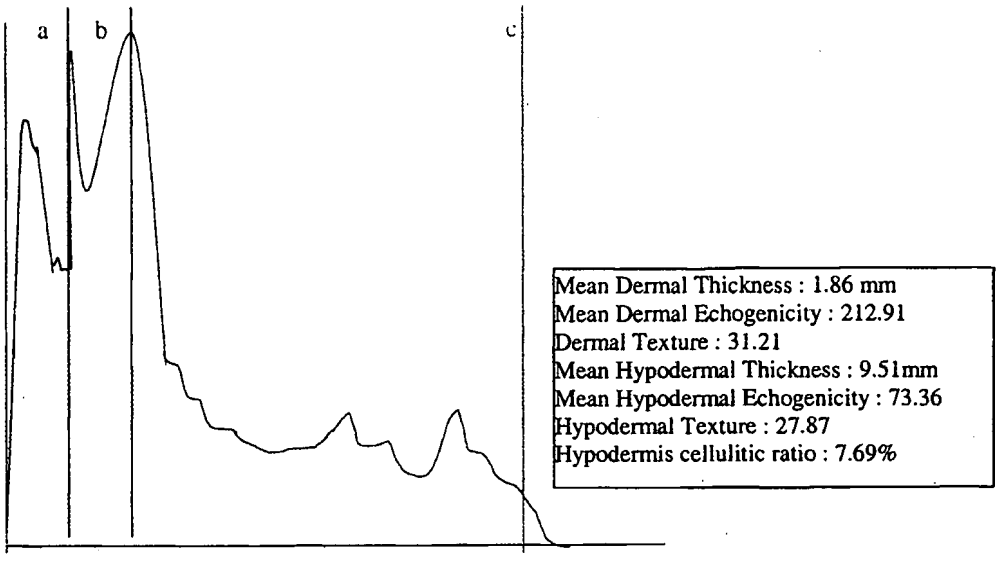

Figure 2. Mean profile of computed image and quantification parameters: Delineation of the different layers allowing calculation of the different parameters.

The studied parameters were:

- Uf: maximum extensibility of the skin (or total deformation)
- Ue: instant vertical extensibility (or elasticity)

(Ue represents the instant deformation of the skin immediately after the application of the strain. This parameter reflects the elastic properties of the skin.)

- Uv: viscoelasticity (or plasticity) extensibility

(Uv represents the delayed deformation of the skin and corresponds to slower deformation due to the intracutaneous movements of viscous type.)

- Ur: immediate retraction (or elastic return)
- Ua: total retraction
- Ur/Uf: biological elasticity

(Ur/Uf reflects the immediate recovering ability of the skin after the end of the strain.)

- Uv/Ue: visoelasticity rate
- Ua/Uf: recovery rate
- R: residual deformation

(R is the residual deformation observed at the end of the "off-time" period. R may be an indicator of the existence of a hysteresa phenomenon.)

4. Flowmetry of the skin perfusion: Laser Doppler flowmetry (8)

Cutaneous blood flow was determined for each thigh by laser Doppler flowmetry using the LISCA PIM II apparatus. Measurements were carried out according to the guidelines edited by the Standardization Group of the European Society of Contact Dermatitis. The measurements were conducted in an air-conditioned room (22+/-2°C, RH 50+/-10%) after 20 minutes of rest period. Skin perfusion was calculated from the image (square area of 6 cm × 6 cm) via the average value of the image's pixels. The homogeneity of the microcirculation of the skin was estimated by the standard deviation calculated from the whole laser Doppler image.

ANALYSIS OF RESULTS

One-way ANOVA and Student's *t*-test were used to determine the significance of the results; the level of significance was set at $p < 0.05$. The comparison between placebo and product was performed on the differences Tx - T0 or on the means when there was no significant difference between the two thighs at T0.

RESULTS

MACRORELIEF OF THE SKIN

With the product, the decrease of the skin macrorelief reached -53.1% at T84 days (versus -14% with the placebo). The improvement of the macrorelief was consistent throughout the study and is statistically significant at each time point. The results obtained are presented Table I.

Table I
Results of the Profilometry Analysis of the Thigh Macrorelief at T28, T56, and T84 Days After the Beginning of the Application (Rz: ratio of effectiveness ± standard deviation)

	T0	T28 days	T56 days	T84 days
Placebo	6.31 (2.41)	5.93 (2.27)	4.91 (1.21)	5.42 (1.86)
Product	6.16 (2.47)	4.48 (1.61)	3.63 (1.46)	2.89 (1.31)

Bold type: significantly different from T0 ($p < 0.05$).

STRUCTURE OF THE DERMIS AND HYPODERMIS

At T84, anomalies of adjustments of the ultrasound apparatus did not permit sequences of analyzable images. Indeed, the dynamics of gray had been regulated the least well and the structures were not sufficiently visible to enter the field of automated quantification. The results obtained (evolution of the placebo and the product between T0 and T28 and between T0 and T56 and comparison between placebo and product) for each of the seven parameters are presented in Table II.

After 28 days of application of the product, the parameters of thickness, echogenicity, and texture of the dermis, and echogenicity and texture of the hypodermis, are significantly improved compared to T0. After 56 days of application, the parameters of texture of the dermis, echogenicity, and texture of the hypodermis are significantly improved compared to T0. As shown Table II, both active and placebo significantly improve the texture of the dermis and the structure of the hypodermis (echogenicity and texture).

MECHANICAL CHARACTERISTICS OF THE SKIN

The results presented in Table III show that the product and the placebo have a significant firming effect; no significant differences could be found between product and placebo.

LASER DOPPLER FLOWMETRY

With the product, at T28 days after the beginning of the applications, an increase of the mean blood flow was observed, which showed a statistical trend at T56 days (38.5%). The increase of the parameter "homogeneity" persisted during the follow-up period, with the increase being statistically significant after one month of application.

The increase in the mean blood flow was greater with the active than with the placebo. With the placebo, this increase was transient and not significant, with a maximum reached at T28 days. The product had a greater and more persistent effect upon the skin microcirculation of the thighs. The same evolution was also observed with the parameter homogeneity (standard deviation of the laser Doppler image). The increase observed with the active product persisted throughout the follow-up period. However, no significant difference was observed between product and placebo. The results are presented in Table IV.

Table II
Results Obtained With the Sonograph 3D on the Structure of the Dermis and Hypodermis: Mean (standard deviation)

Time (days)	Product	Dermis thickness	Dermis echogenicity	Dermis texture	Hypodermis echogenicity	Hypodermis texture	Fat ratio	Interface (dermis/ hypodermis)
T0	Placebo	1.95 (0.28)	208.25 (11.74)	22.43 (3.26)	44.41 (9.59)	21.45 (2.79)	19.26 (4.68)	1.83 (0.31)
	Product	1.94 (0.23)	208.49 (11.95)	22.13 (3.72)	44.71 (8.77)	21.04 (2.40)	18.56 (4.70)	1.80 (0.26)
T28	Placebo	1.90 (0.27)	212.89 (10.80)	25.73 (4.64)	46.86 (11.60)	24.16 (3.91)	18.71 (6.29)	1.74 (0.20)
	Product	1.86 (0.24)	214.07 (9.13)	25.97 (4.01)	46.98 (9.40)	23.64 (3.72)	18.46 (4.96)	1.76 (0.23)
T56	Placebo	1.90 (0.23)	199.69 (9.64)	31.78 (6.38)	50.28 (12.23)	30.00 (5.32)	17.03 (9.92)	1.76 (0.26)
	Product	1.97 (0.28)	197.38 (12.79)	33.64 (7.04)	50.37 (14.94)	30.41 (4.92)	16.88 (9.39)	1.80 (0.22)

Bold type: significantly different from T0 ($p < 0.05$).

Table III

Results Obtained for the Different Parameters Describing the Mechanical Properties of the Skin (mean and standard deviation)

Time (days)	Product	Uf	Ue	Uv	Ur	Ua	R	Ur/Ue	Uv/Ue	Ur/Uf	Ua/Uf
T0	Placebo	1.093	0.903	0.167	0.891	0.990	0.091	0.980	0.188	0.812	0.904
		(0.123)	(0.118)	(0.022)	(0.188)	(0.133)	(0.022)	(0.130)	(0.031)	(0.130)	(0.081)
	Product	1.118	0.925	0.167	0.920	1.019	0.081	0.992	0.184	0.821	0.910
		(0.138)	(0.128)	(0.025)	(0.173)	(0.143)	(0.057)	(0.112)	(0.038)	(0.110)	(0.054)
T28	Placebo	1.050	0.859	0.157	0.820	0.917	0.119	0.949	0.186	0.777	0.872
		(0.115)	(0.109)	(0.023)	(0.171)	(0.140)	(0.088)	(0.134)	(0.032)	(0.124)	(0.076)
	Product	1.050	0.873	0.143	0.829	0.922	0.112	0.947	0.167	0.786	0.876
		(0.135)	(0.126)	(0.023)	(0.166)	(0.144)	(0.073)	(0.113)	(0.034)	(0.105)	(0.059)
T56	Placebo	0.966	0.766	0.166	0.790	0.874	0.074	1.035	0.224	0.819	0.906
		(0.119)	(0.113)	(0.022)	(0.140)	(0.116)	(0.070)	(0.134)	(0.047)	(0.112)	(0.059)
	Product	0.974	0.780	0.156	0.807	0.881	0.071	1.038	0.205	0.828	0.904
		(0.130)	(0.123)	(0.020)	(0.146)	(0.128)	(0.063)	(0.131)	(0.037)	(0.109)	(0.053)
T84	Placebo	0.991	0.778	0.177	0.848	0.916	0.062	1.094	0.234	0.857	0.925
		(0.104)	(0.098)	(0.027)	(0.139)	(0.103)	(0.075)	(0.134)	(0.046)	(0.114)	(0.052)
	Product	0.982	0.781	0.165	0.836	0.905	0.068	1.071	0.219	0.848	0.922
		(0.136)	(0.130)	(0.019)	(0.152)	(0.128)	(0.082)	(0.152)	(0.043)	(0.126)	(0.058)

Bold type: significantly different from T0 ($p < 0.05$).

Table IV
Results Obrained by Laser Doppler Flowmetry (mean and standard deviation)

Microcirculation		T0	T28 days	T56 days	T84 days
Mean value	Placebo	0.094 (0.009)	0.117 (0.013)	0.112 (0.011)	0.095 (0.008)
	Product	0.096 (0.008)	0.132 (0.021)	0.133 (0.017)	0.121 (0.026)
Homogeneity	Placebo	0.160 (0.019)	0.244 (0.038)	0.166 (0.015)	0.157 (0.014)
	Product	0.156 (0.014)	**0.237 (0.035)**	0.222 (0.045)	0.223 (0.054)

Bold type: significantly different from T0 ($p < .0.05$).

DISCUSSION

The effect of the association of retinol, caffeine, and ruscogenine in an alcoholic vehicle was tested by a unique combination of objective non-invasive methods. It allowed visual and measurable results on several parameters.

The results clearly show a significant benefit of the product versus placebo for the microrelief and the microcirculation parameters. The echogenicity and the texture of the dermis as well as the mechanical properties of the skin were improved with the two products versus baseline.

The placebo effect might be explained by two factors. First, massage by itself can have a beneficial action on cellulite since massage has been shown to accelerate blood flow and prevent fibrosclerosis (1). Second, the ethanol that was used with the placebo in order to obtain the same cosmetic feeling on application can also be an adipo-kinetic substance like noradrenaline and induce qualitative changes in plasma non-esterified fatty acids (9,10). Further studies where the placebo is devoid of ethanol should be performed in order to evaluate the actual role of ethanol in cellulite.

The macrorelief assessed by profilometric measurement was significantly improved by the active product compared to the placebo. This activity is likely to be linked to the improvement of the other measured parameters: dermal and hypodermal structures, skin firmness, and indirectly, skin microcirculation. This efficacy can be explained by the chosen active ingredients that have been described by several authors.

The lipolytic activity of caffeine has been known for a long time (11). It is related to an inhibition of phosphodiesterase, which transforms the active cAMP into inactive 5'AMP. The resulting increase in cAMP stimulates the degradation of triglycerides into fatty free acids by the triglyceride lipase, therefore inhibiting fat accumulation. However, different studies (12) have demonstrated that the lipolytic action of caffeine also results from a synergy with the catecholamines present in the adipose tissue that stimulate peripheral lipolysis by acting on the adrenalino-sensitive lipase (Figure 3).

Ruscogenine extract has demonstrated a remarkable inhibition of elastase (13). This inhibition can promote the recovery of extracellular matrix integrity, resulting in an improvement in nutriment exchange between the microcirculatory system and the ground substance. Indeed, according to some authors, the lack of communication between the cells and the ground substance is responsible for the process of cellulite (12).

Ruscogenine extract presents a tonic effect on blood vessel tone by an adrenergic-type action. This effect can be direct (agonist of the adrenergic receptors of the smooth cells) or indirect (noradrenaline liberation) (12). This activity has been associated with a

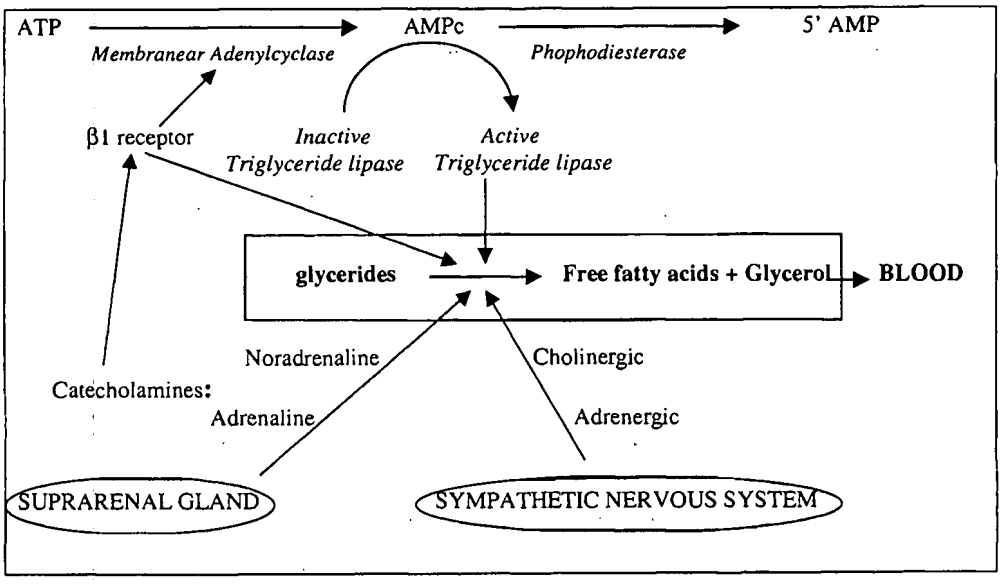

Figure 3. Mechanisms acting on lipolysis (enzymatic, nervous, and suprarenal).

significant increase in lymphatic and venous flow, with a reduction in capillary permeability (12).

More recently, retinol has been shown to have a beneficial effect on cellulite (4,14). This effect might result from the action of retinol on dermal collagen deposition, improving both thickness and firmness of the dermis (14–16). A direct effect of retinol on preadipocytes has also been demonstrated recently, since the exposure of cultured human preadipocytes to retinol results in a marked reduction in the differentiation of the fat cells and a decrease in the number of mature adipocytes (17).

The different methods used allowed us to detail the activity of the product compared to baseline and placebo. The assessment of the dermal-hypodermal structure conducted by a novel method allowed us to characterize skin texture during the use of the two products (active product and placebo) and, therefore, to assess a possible result of the product activities on the dermis and hypodermis. The skin firmness improvement observed with the two products, measured conventionally, is probably due, in great part, to the massage, because the placebo increases it at the same level as the product. The flowmetry of skin perfusion was more improved with the product than with the placebo. This activity may be explained by the presence of ruscogenine extract (12,13).

CONCLUSION

The association of the three tested active ingredients was significantly active on the "orange peel" appearance of the skin, which is the most apparent manifestation of cellulite (53.1% at T84 versus 14.1% for the placebo). The skin microcirculation, whose dysfunction is involved in the pathophysiology of cellulite, was also significantly and durably improved by the product, compared to the placebo. The combination of these different methods allowed measurement of different skin parameters, which change

according to the appearance of cellulite, and demonstrated a measurable activity for the active product.

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CONTENTS

Advances In Natural Therapy™

HCI Health Communications Inc

Original Contribution

A two-center, double-blinded, randomized trial testing the tolerability and efficacy of a novel therapeutic agent for cellulite reduction

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Summary

Introduction Cellulite is the unsightly dimpling and nodularity found on the thighs and buttocks of many postadolescent women. Unfortunately, poor understanding of its pathophysiology coupled with very few scientifically based studies have left us with limited treatment options that are tolerable and effective.

Purpose To review current concepts of the etiology and nature of cellulite and summarize available treatment options. To evaluate a novel, pathophysiologically based, topical agent for treatment.

Materials and methods A total of 40 women with a moderate degree of cellulite (20 from each of the two research centers) entered a double-blinded, randomized trial where an anticellulite cream was applied on a nightly basis to the affected sites for four continuous weeks. Each subject was randomized to receive active cream on either the right or left leg, with the contralateral side serving as placebo control. Bioceramic-coated neoprene shorts were worn overnight to enhance penetration of the topical agents by occlusion. High-quality digital photography was taken before treatment and after 4 weeks, with tangential full-spectrum lighting. Five blinded, independent physician reviewers assessed the photographs for improvement. Subject questionnaires were completed to assess tolerability and efficacy.

Results Of the 34 subjects who completed the study, 62% (21/34) noticed an overall improvement in their cellulite, with 62% (13/21) reporting greater improvement in the thigh that received active product. All 34 subjects found the shorts and creams easy and pleasant to use. Overall, the average measured decrease in thigh circumference was 1.9 cm (range: 0.1–4.5) with active product, and 1.3 cm (range: 0.1–3.0) with placebo. Upon review of the pre- and poststudy photographs, dermatologist evaluators found thighs treated with active product showed greater improvement than thighs treated with placebo in 68% of subjects.

Conclusions The active topical agent used in this study was found to be effective in reducing the appearance of cellulite. All subjects tolerated the formulation well with no adverse effects. The success of this research validates the pathophysiologic concepts used to formulate the topical compound. This study both increases our understanding of the nature of cellulite and establishes a tolerable, effective product to treat it.

Keywords: cellulite, topical agent

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Introduction

Historically a sign of beauty and wealth, the presence of cellulite is now considered aesthetically objectionable. Cellulite is the unsightly skin dimpling frequently seen on the thighs and buttocks of women, regardless of body shape and size. It is estimated that 85% of women over age 20 have some degree of cellulite.[1–3] Tremendous resources and effort are continually being directed to develop topical agents, internal supplements, exercise and diet programs, massage, and even surgery to cure this problem. The degree to which any of these remedies is effective in cellulite clearance or reduction remains questionable.

The pathophysiology of cellulite is poorly understood, and a literature review demonstrates a paucity of studies to scientifically validate currently popular treatments.

This article describes the evaluation of a novel topical agent specifically designed to reduce cellulite. As well, a thorough review of the literature is presented, summarizing current concepts of the origin and nature of cellulite and available therapeutic options.

Materials and methods

Twenty healthy adult women with moderate to severe cellulite (cellulite score of at least II out of IV) were selected for enrolment at each of the two sites after assessment by a physician investigator. This was performed against a solid black background and tangential full spectrum lighting delivered from the Verilux Happy Lite™ system (Verilux Inc, Stamford, Connecticut) without additional ambient lighting. The tangential lighting system was always positioned 2 feet from the subject, parallel to the backdrop at the level of the subject's knees.

Exclusion criteria included:

- treatment for cellulite of the thighs within 1 month of the study period;
- history of deep vein thrombosis within the past 2 years;
- history of congestive heart failure;
- occlusive arterial disease of the legs;
- pregnant or lactating women;
- history of topical medication usage (especially corticosteroids) within 2 weeks of the study period;
- history of allergic contact dermatitis to any component of the bioceramic-coated neoprene garment.

Upon enrollment, consent forms, bill of rights for medical subjects, photography release forms, and the Health Insurance Portability and Accountability Act (HIPAA) were reviewed and signed. High-quality color digital photographs were then taken of the posterior and lateral thighs by an investigator trained to use the Fuji S1 Twinflash™ Camera system (Canfield Inc, Fairmont, New Jersey). All photos were taken in the same room and utilizing the same methodology as described during the physician assessment. Three photos were taken at the following angles:

(a) 90° right thigh
(b) 45° right thigh
(c) 180° right thigh
(d) 90° both thighs
(e) 90° left thigh
(f) 45° left thigh
(g) 180° left thigh

Thigh circumference measurements were then taken of both legs at 18 cm and 26 cm from the superior pole of the patella for the lower and upper thigh, respectively, using a flexible measuring ruler.

After all data were collected, the subject was fitted with appropriately sized bioceramic-coated neoprene shorts. Subjects were previously randomized to have either the right leg or the left leg treated by the active agent, a specifically designed anticellulite cream (Spa MD Anti-Cellulite Cream™, La Jolla, California) and placebo cream for the contralateral leg. Subjects were blinded as to which cream, either active or placebo, they received, as containers were stripped of all labels and marked randomly as either "A" or "B". The quantities of creams dispensed to each subject were two 60-g tubes of anticellulite cream and two 60-g tubes of placebo. Patients were instructed to apply the appropriate cream to the posterior and lateral aspects of the corresponding thighs from the level of the knee to the buttock on a daily basis. The bioceramic neoprene shorts were to be worn immediately after application of the creams for at least 6 h (ideally while the subject slept). Figure 1 illustrates an example of how the garment appears when worn correctly. Treatment duration was 4 weeks. All unused active product and placebo creams were returned at the follow-up visit to ensure subject compliance.

At the 4-week follow-up, inclusion and exclusion criteria were reviewed to ensure continued enrollment. Each subject was then asked to complete a self-evaluation survey and give feedback regarding their experiences with the creams and shorts. Subjects were also asked to comment on the ease of use and tolerability of the creams and shorts. High-quality digital photography and thigh circumference measurements were taken using the same protocol as the baseline photography and measurements (see Figures 2 and 3).

All photographs were compiled and reviewed by five blinded, independent board-certified dermatologists. The evaluators were shown two pairs of photos for each subject: (1) pre- and post-treatment photographs of a subject's right thigh, and (2) pre- and post-treatment photographs of the same subject's left thigh, blinded to which side received active *vs.* placebo cream. After close

Figure 1 The bioceramic-coated neoprene shorts, worn after topical application to the posterior and lateral thighs to provide greater penetration into the skin by occlusion.

inspection, the evaluators then determined which thigh, the left or the right, showed greater improvement in cellulite.

All results were tabulated and analyzed.

Results

Thirty-four of the 40 enrolled subjects completed the 4-week study, and were compliant with the study methodology. Subjects ranged in age from 26 to 74 years (mean 49 years). At the La Jolla site, one patient withdrew from the study because of an unrelated yeast infection, and one was lost to follow-up. At the Nashville site, four patients were lost to follow-up. Table 1 summarizes the results of subject questionnaires. Of the subjects who completed the study, 62% (21 out of 34) noticed an overall improvement in cellulite. Of the 21 subjects that noticed an improvement in cellulite, 62% (13 out of 21) reported a greater improvement on the leg that received active product. The remaining 38% (8 out of 21) reported an equal degree of improvement in both legs.

All 34 subjects who completed the study found the shorts and creams easy to use. These subjects all reported having enjoyed using both the placebo and anticellulite cream. Many found both to have a softening and smoothening effect and appealing fragrance. In general, subjects were unable to determine the difference between active product and placebo based on the characteristics of the agents themselves. Some subjects reported the bioceramic-coated neoprene shorts to have generated warmth. Most enjoyed this warm sensation, while the others found it somewhat uncomfortable. At the conclusion of the study, many subjects elected to continue to use the anticellulite cream and occlusive shorts on a regular basis.

Thigh circumference measurements and analyses are presented in Table 2. Of subjects who completed the study, thigh circumference measurements decreased in 74% (25 out of 34) treated with active product, and in 56% (19 out of 34) who received placebo. The average decrease in circumference of the lower thigh treated with

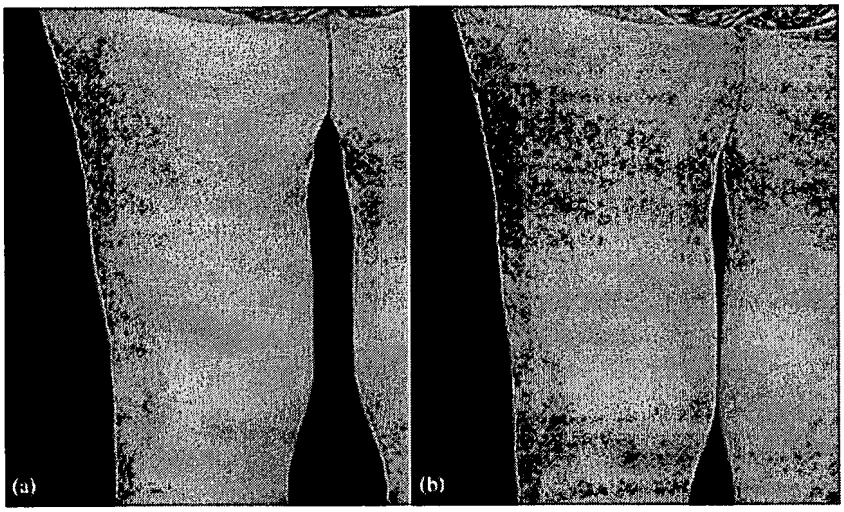

Figure 2 Photographs taken (a) immediately before and (b) 4 weeks after daily use of the anticellulite cream with occlusion by a bioceramic-coated neoprene garment.

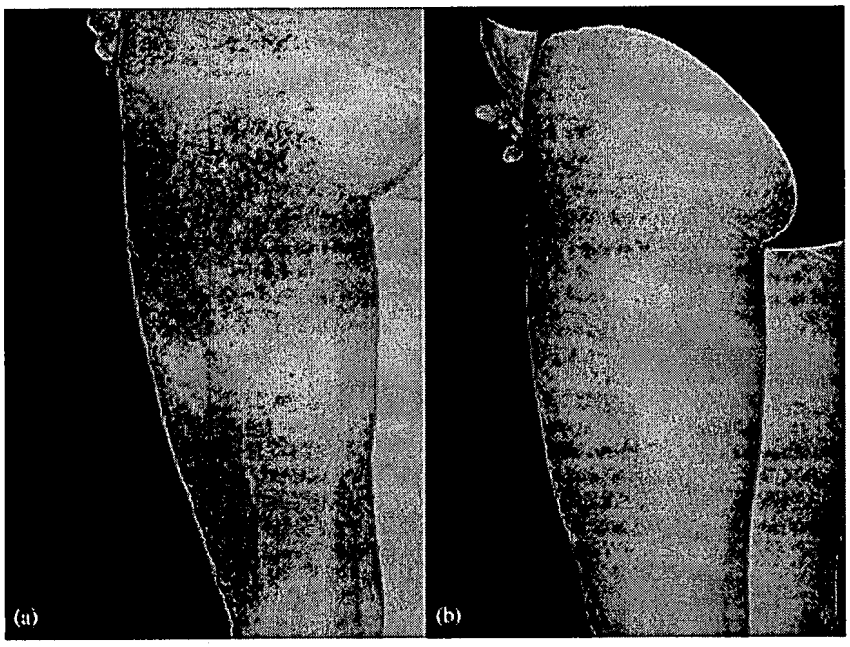

Figure 3 Photographs taken (a) immediately before and (b) 4 weeks after daily use of the anticellulite cream with occlusion by a bioceramic-coated neoprene garment.

active product was 2.08 cm (range: 0.1–3.5), and 1.04 cm (range: 0.1–2.5) treated with placebo. The average decrease in circumference of the upper thigh treated with active product was 1.78 cm (range: 0.1–4.5), and 1.50 cm (range: 0.3–3.0) treated with placebo. Overall, the average measured decrease in thigh circumference was 1.93 cm (range: 0.1–4.5) with active product and 1.27 cm (range: 0.1–3.0) with placebo.

Table 3 summarizes the results of the pre- and post-study photographic evaluations by five blinded, independent board-certified dermatologists. Overall, improvement in cellulite was seen in legs treated with active product in 68% of subjects. Standard deviation in scoring between evaluators was 0.89 at the La Jolla site and 1.14 at the Nashville site, indicating close correlation of scores.

Discussion

Definition and nature of cellulite

The term "cellulite" is used in modern times to describe the dimpled or puckered skin of the posterior and lateral thighs and buttocks seen in many trim and overweight women. The appearance is often described to resemble the surface of an orange peel or that of cottage cheese. The condition is best described by Goldman as a normal physiologic state in postadolescent women, which maximizes adipose retention to ensure adequate caloric availability for pregnancy and lactation.[4] Adipose tissue is also essential for nutrition, energy, support, protection, and thermal insulation.[5] At the histological level, cellulite is the result of localized adipose deposits and edema within the subcutaneous tissue. In women, longitudinal fibers of connective tissue fascia segregate fat into channels resembling a *down quilt*. As the fat layer expands, the perpendicular connective tissue remains fixed, creating a superficial puckered appearance of the skin.[5–8] This skin dimpling is rarely found in men as the connective tissue in males is arranged in a criss-crossing pattern that is gender-typical for the skin of the thighs and buttocks.[5,7]

Predisposing factors

There are many predisposing factors that contribute to cellulite development. These include:

- gender: because of the underlying structure of fat and connective tissue described previously, women are more likely to develop cellulite;
- heredity: empirically, it has been found that the degree and presence of cellulite, as with body habitus, is often similar between females within the same family;
- race: Caucasian women are more likely to develop cellulite than Asian or African American women;[9]
- increased subcutaneous fat: because of the unique histology of skin with cellulite, it is evident that greater adipose tissue in the subcutaneous layer enhances the appearance of cellulite on the skin surface;[10]
- age: women begin to develop cellulite after puberty as part of normal anatomical and physiological development.

Table 1 Study results based on subject questionnaires.

A) La Jolla site

- 72% (13 out of 18) of patients noticed an overall improvement in cellulite
- 62% (8 out of 13) of patients who noticed an improvement in cellulite reported a greater improvement on the leg that received active product
- 38% (5 out of 13) of patients noticed the same amount of improvement in the leg treated with active product compared with the placebo-treated leg
- 100% (18 out of 18) of patients reported to have enjoyed using the anticellulite cream

B) Nashville site

- 50% (8 out of 16) of patients noticed an overall improvement in cellulite
- 62% (5 out of 8) of patients who noticed an improvement in cellulite reported a greater improvement on the leg that received active product
- 38% (3 out of 8) of patients noticed the same amount of improvement in the leg treated with active product compared with the placebo-treated leg
- 100% (16 out of 16) of patients reported to have enjoyed using the anticellulite cream

C) Combined data

- 62% (21 out of 34) of patients noticed an overall improvement in cellulite
- 62% (13 out of 21) of patients who noticed an improvement in cellulite reported a greater improvement on the leg that received active product
- 38% (8 out of 21) of patients noticed the same amount of improvement in the leg treated with active product compared with the placebo-treated leg
- 100% (34 out of 34) of patients reported to have enjoyed using the anticellulite cream

Unfortunately, these predisposing factors are difficult if not impossible to alter, thus cellulite prevention is currently not attainable. However, based on our understanding of the etiology and nature of this condition, several treatment modalities have been developed.

Pathophysiology of cellulite

Hormones, specifically estrogens and androgens, are thought to influence the formation of cellulite. Estrogen is known to stimulate lipogenesis and inhibit lipolysis, resulting in adipocyte hypertrophy.[9] This may explain the onset of cellulite at puberty, the condition being more prevalent in females, and the exacerbation of cellulite with pregnancy, nursing, menstruation, and estrogen therapy (oral contraceptive use and hormone replacement).[9] The opposite seems true for men. From the limited number of studies involving men, it is hypothesized that the combination of gender-specific soft tissue histology at the cellulite-prone anatomic sites, with a relatively lower circulating estrogen level, may be responsible for the lower incidence of cellulite in males.[10,11] It may be that circulating androgens have an inhibitory effect on cellulite development by contributing to a different pattern of adipose tissue storage (that is, more truncal than on the buttocks and thighs). As such, regulation of hormone levels may help to minimize the appearance of cellulite. Unfortunately, this treatment option may result in adverse physiological and anatomical sequelae, and has therefore not been widely employed.

Adipose tissue is very vascular, leading to the theory that cellulite may develop in predisposed areas when circulation and lymphatic drainage have been decreased, possibly caused by local injury or inflammation. It is known that in response to impairment of microvascular circulation, there is increased microedema within the subcutaneous fat layer, causing further stress on surrounding connective tissue fibers and accentuation of skin irregularities.[2,4] Many of the currently accepted cellulite therapies target deficiencies in lymphatic drainage and microvascular circulation.

Evaluation of cellulite

There is a broad spectrum of tools available to evaluate cellulite, ranging from simple observation to tissue biopsy. Such methods include:

- observation: this involves direct or photographic visualization of skin irregularities such as puckering, dimpling, and nodularities. Observation is best performed in a dark room with tangential lighting to create shadows that represent even subtle surface elevations and depressions. Gently squeezing the skin under these lighting conditions may accentuate less apparent tethering of the skin.
- weight or body mass index (BMI; weight in kilograms divided by height in meters, squared): this is a generalized estimate of body composition used to assess obesity based on a population average.[9] BMI is not an effective evaluative tool for cellulite as it does not correlate to either cellulite content or distribution.
- thigh circumference: the measure of thigh circumference at set points with a flexible ruler can give an indirect measurement of localized fat and possibly cellulite related to this. Unfortunately, changes in thigh circumference may be as a result of a host of other factors, including edema from congestive heart disease, trauma

Table 2 Changes in thigh circumference following a continuous 4-week application of a specifically designed anticellulite cream *vs.* placebo.*
A) La Jolla site

	With active cream		With placebo	
Subject	Lower thigh (cm)	Upper thigh (cm)	Lower thigh (cm)	Upper thigh (cm)
1	None†	None	None	None
2	−3.3	−1.3	−0.4	−0.3
3	−3.5	−1.5	−0.1	−1.0
4	Patients did not complete study			
5	None	None	None	None
6	None	None	None	None
7	−0.1	−0.4	None	None
8	−0.5	−0.1	None	None
9	−1.8	−2.4	−0.5	−0.8
10	None	None	None	None
11	Patient did not complete study			
12	None	None	None	None
13	−3.0	−4.5	−1.5	−1.0
14	−1.6	−3.5	−0.5	−3.0
15	−2.4	−1.8	−0.2	−0.4
16	None	None	None	None
17	−1.2	−0.9	None	None
18	−2.8	−1.8	−0.5	−0.9
19	−2.5	−3.3	−1.2	−1.5
20	−0.3	−2.7	None	None
Average	**−1.92**	**−2.02**	**−0.61**	**−1.11**

*Recordings were taken at 18 cm and 26 cm above the superior pole of the patella for lower and upper thigh measurements, respectively. All creams were administered under occlusion.
†No reduction in thigh circumference was noted.

B) Nashville site

	With active cream		With placebo	
Subject	Lower thigh (cm)	Upper thigh (cm)	Lower thigh (cm)	Upper thigh (cm)
1	Patient did not complete study			
2	−1.9	−2.5	−1.3	None†
3	−3.8	−1.9	None	None
4	−1.9	−1.3	−1.3	None
5	−1.9	−2.5	None	None
6	Patient did not complete study			
7	−0.6	None	−0.6	None
8	−2.5	−0.6	−1.3	−2.5
9	−2.5	−1.3	−2.5	−2.5
10	−3.2	−1.9	None	−1.3
11	−1.9	None	−2.5	None
12	−1.3	None	−1.3	None
13	None	None	−1.9	−1.9
14	Patient did not complete study			
15	Patient did not complete study			
16	None	None	−1.3	−2.5
17	None	−0.6	None	−1.3
18	−3.2	None	None	None
19	None	−1.3	−0.6	−1.3
20	None	None	None	None
Average	**−2.24**	**−1.54**	**−1.46**	**−1.90**

*Recordings were taken at 18 cm and 26 cm above the superior pole of the patella for lower and upper thigh measurements, respectively. All creams were administered under occlusion.
†No reduction in thigh circumference was noted.

Table 2 *Continued.*
C) Combined data

	With active cream		With placebo	
	Lower thigh (cm)	Upper thigh (cm)	Lower thigh (cm)	Upper thigh (cm)
La Jolla site	−1.92	−2.02	−0.61	−1.11
Nashville site	−2.24	−1.54	−1.46	−1.90
Average	**−2.08**	**−1.78**	**−1.04**	**−1.50**
Overall average	**−1.93**		**−1.27**	

Table 3 Visual improvement of cellulite after 4 weeks of active product *vs.* placebo, as observed by blinded, independent dermatologist evaluators.
A) La Jolla site

Evaluator	Number of subjects showing greater improvement with active product
1	13/18 (72%)
2	14/18 (78%)
3	13/18 (72%)
4	15/18 (83%)
5	13/18 (72%)
Average	**13.6/18 (76%), STD = 0.89**

B) Nashville site

Evaluator	Number of subjects showing greater improvement with active product
1	8/16 (50%)
2	10/16 (62%)
3	11/16 (69%)
4	9/16 (56%)
5	9/16 (56%)
Average	**9.4/16 (59%), STD = 1.14**

C) Combined data

Site	Number of subjects showing greater improvement with active product
La Jolla	13.6/18 (76%)
Nashville	19.4/16 (59%)
Overall	**23/34 (68%)**

or lymphatic impairment, and inflammation from various conditions and external sources. Also, thigh circumference may vary rapidly with activity and exercise, resulting in varying measurements between evaluation sessions.

- skin elasticity: measurement of skin tension with a suction elastometer can give an estimate of the resilience of the dermis, a function of connective tissue helping to gauge the amount of cellulite present. In theory, this tool may be plausible, but to date, clinically useful results remain to be seen;
- electrical conductivity: this is used to measure tissue resistance to electron flow and determine specific percentages of body composition (lean mass, fat mass, water).[9] Whether cellulite content affects these measurements also remains to be seen;
- tissue analysis from a deep skin biopsy of affected areas: this method is the most specific modality to determine the presence of cellulite histologically. However, even though tested tissue may have the microscopic characteristics of cellulite, the clinical appearance may not correlate with this. Conversely, clinically present cellulite may reveal the histology of normal skin.

Of all these methods to examine cellulite, observation with tangential lighting, and anthropometric measurements are the most common because of their fair reproducibility, relative accuracy, ease, and cost effectiveness.

Classification

To accentuate cellulite dimpling in an effort to classify the degree of severity, it is best to gently pinch an area of

Table 4 Cellulite classification.

Grade I	No or minimal cellulite based on observation when standing, the pinch test, or gluteal muscle contraction.
Grade II	Irregular skin topography upon observation. Cellulite is enhanced by pinching or gluteal contraction. Subjects may have skin pallor or decreased temperature and sensation.
Grade III	Skin exhibits the classic orange peel dimpling, "peau d'orange," at rest. Small subcutaneous nodularities may be palpated.
Grade IV	In addition to the characteristics described above there is more severe puckering and palpable nodules.

tissue between the fingers and the thumb. For larger areas, the skin of the thigh can be compressed between two hands. This is referred to as the *mattress phenomenon* as the dimpled pinched skin resembles a bed mattress. Cellulite may be graded for severity on a scale of I to IV (see Table 4).[4,9,12]

Management

There is currently no cure or gold standard for treatment of cellulite. This is due in part to the minimal understanding of cellulite pathophysiology and poor therapeutic effectiveness of most treatment modalities. Therapeutic options to manage cellulite can be characterized as conservative measures, topical treatment, systemic agents, and physical modalities.

Conservative management includes the adoption of a healthy lifestyle. Unfortunately, there is little evidence to support dramatic cellulite reduction with the combination of diet and regular exercise. Diet and exercise cannot alter the histological structure of the perpendicular bands connecting the skin to the underlying fascia and thus cannot eliminate cellulite in its entirety. However, these lifestyle modifications may assist in reducing the appearance of cellulite by decreasing adipocyte volume, thus placing less tension on surrounding connective tissue, resulting in decreased skin puckering.

Topical management consists of gels, ointments, foams, creams, and lotions, all aimed to deliver active product to the skin to reduce the appearance of cellulite. Most active ingredients, including antioxidants and vasodilators, are included to increase microvascular flow and lymphatic drainage, which is thought to play a role in cellulite pathogenesis. Other agents may promote lipolysis, with the goal of reducing the size and volume of adipocytes, thereby decreasing tension on surrounding connective tissue and decreasing the clinical appearance of puckering. Some topical ingredients, such as vitamin C, may help by stabilizing collagen and/or stimulating collagen deposition.[3,4,9] Topical retinoic acid and related vitamin A derivatives have been used to stimulate circulation, decrease the size of adipocytes, and increase collagen deposition in the dermis.[9,13] In reality, however, vitamin A derivatives have not provided an ultimate solution to reduce the unshapely appearance of cellulite.

Systemic therapy in the form of hormonal manipulation is not a popular treatment option because of its many potential adverse effects. This may include the avoidance of oral contraceptives and hormone replacement in females and the maintenance of proper androgen levels in males. The opposite situation has been shown to be associated with the presence of relatively more cellulite.[10,11] An even more aggressive systemic treatment option is the direct injection of pharmacologic agents into the venous circulation, or local infiltration into the dermal-subcutaneous junction of the skin. This is referred to as *intradermotherapy* or *mesotherapy*, and reduces cellulite through lipolysis of fat or size reduction of adipocytes.[9] Studies to demonstrate the safety and efficacy of this therapeutic modality have yet to be published.

Physical therapies vary widely from noninvasive modalities such as Endermologie® (LPG Systems, Valence, France) to surgical procedures including deep subcision and liposculpture. Endermologie® is a French-designed form of deep-tissue massage that the United States Food and Drug Administration (FDA) has approved to diminish the appearance of cellulite. During the massage, suction is used to pull the skin into a handheld machine where the skin is compressed and rolled to increase blood and lymphatic flow and to modify the underlying connective tissue.[2] This therapy is performed in a series of 30–45-min sessions over a period of months. The cellulite-minimizing effect of all forms of deep-tissue massage is temporary and therapy must be continued to maintain results.

A new laser device recently approved by the FDA combines variable rhythmic suction with superficial cooling and a low intensity 808-nm diode laser pulsation to treat cellulite. This technology, labeled Triactive™ (Cynosure, Chelmsford, Massachusetts) was designed to increase lymphatic drainage, tighten the skin by stimulating underlying muscles and fascia, and increase superficial blood flow, thereby reducing the appearance of cellulite. Treatment regimen mimics that of Endermologie®, with greater emphasis directed toward the proposed microcirculation impairment theory of cellulite formation. Although Triactive™ has been proven safe and easy to use, its efficacy in treating cellulite remains to be seen, as research is ongoing.

Subcision is a simple surgical procedure that has been noted to improve moderate to severe cellulite.[12] With the use of local anesthesia, this technique is performed by inserting a notched catheter (such as a Nokor™ needle) into the subcutaneous layer of the skin. The catheter is then manually moved in a repetitive motion parallel to the surface to physically break the connective tissue adhesions that tether the dermis to muscular fascia. Upon rupture of these adhesions, the tethering effect is diminished and cellulite improved. Although reported successful, it is unclear if these beneficial results are long-term, and if not, how long remission time lasts.

Liposculpture involves the removal of local adipose tissue deposits to achieve a greater aesthetic body contour. Performed under general or local tumescent anesthesia, this surgery uses a small tip suction cannula to remove fat from unwanted areas, without altering other skin tissues. Adipose tissue is most commonly extracted from the thighs, buttocks, abdomen, back, face, neck, and arms. Liposculpture

may decrease the appearance of cellulite by reducing local fat volume and by disrupting the fibrous bands that cause the dimpling appearance of the skin surface. The procedure will not, however, permanently eliminate cellulite. It is possible that a combination of liposculpture with other modalities such as Triactive™ may work in synergy to prolong the effects of cellulite reduction. Studies are currently being conducted to verify this hypothesis.

The present study

With the paucity of research that currently exists to aid our understanding of cellulite and its treatment, this study evaluates a novel topical agent specifically designed to remedy the most correctable pathophysiologic mechanism of the condition.

Based on the concept of microcirculatory and lymphatic impairment outlined in this review, an anticellulite cream was formulated. Table 5 lists the active ingredients of this formulation according to their proposed mechanism of action. In contrast, the placebo cream contained vehicle only, and notably lacked these active ingredients. It is likely that the active agents act through vasodilation of capillaries and microlymphatics. Caffeine may work through a variety of mechanisms including the improvement of vascular and lymphatic flow through vasodilation, as well as by lipolysis. The combination of mechanisms of caffeine may be responsible for noted decreases in thigh circumference.[14] The bioceramic-coated neoprene garments were designed to offer maximal occlusion against the skin even during motion. Warmth and external pressure from wearing the garment likely improves absorption, which allows the anticellulite cream to penetrate the dermis, thereby improving efficacy. A tangential lighting system was employed using full-spectrum white lights to accentuate cellulite-related elevations and dimples on the skin surface, without color distortion. Standardization of photography was employed to maximize reproducibility of picture brightness and clarity, as well as anatomic positioning of the subject.

Table 5 Proposed active ingredients of the anticellulite cream used in this study.

Stimulation of lymphatic and microvascular flow
• *Piper nigrum* (black pepper) seed extract
• *Citrus aurantiu dulcis* (sweet orange) peel
• *Zingiber officinale* (ginger) root extract
• *Camellia sinesis* (green tea) extract
• *Cinnamomum cassia* (cinnamon) bark extract
• *Capsicum annum* resin
• Caffeine
Lipolysis of adipose tissue
• Caffeine

The results demonstrate that the anticellulite cream is indeed effective and tolerable, both subjectively and objectively (see Tables 1–3). This study was designed to have each subject serve as her own internal control. If daily weight or fluid changes occurred, it would likely affect the active cream group and the placebo cream group equally. Possible sources of error in this study include inter- and intrauser variability in thigh measurements to establish pre- and post-treatment thigh circumference. In addition, daily fluctuations in subcutaneous fluid may occur, contributing to a perceived change in thigh circumference, rather than by cellulite reduction. This study relies heavily upon subject compliance, both in terms of application of appropriate amount of cream to designated anatomic sites, as well as the judicial use of the occlusive garment as outlined in the study protocol. Any deviation or lack of consistency on the part of the subject in this regard may have affected study results. Other contributory factors to error are possible fluctuation of subject weight caused by changes in diet and exercise during the 4-week study. Also, each site utilized a different team of researchers to obtain thigh measurements. However, the same five dermatologists assessed all photographs. The use of photography, although of high quality, is not a perfect substitute for direct physical examination, a point that may contribute to variable scores between evaluators.

This study demonstrates that a topical agent based on current mechanistic knowledge of cellulite formation can be used to treat this unwanted condition. A study of longer duration and more subjects would be useful in establishing the long-term efficacy of this therapy. Perhaps an in-depth analysis of individual components of the cream may reveal that ingredients previously thought to be active are in fact not contributory to the anticellulite effect of the cream as a whole. Conversely, it is possible that the addition of new ingredients to the formulation may enhance the effect of the cream. Of note, the fact that improvement was subjectively and objectively demonstrated with placebo indicates that the occlusive garments not only assisted in drug delivery, but also independently served as a topical treatment for cellulite reduction.

Conclusion

With the proven tolerability and efficacy of this topical agent in improving cellulite, several implications are manifested. First, this formulation offers a valuable treatment option for a condition that has few effective therapeutic choices. Second, with this treatment based on the theory that

microcirculatory and lymphatic impairment is contributory to cellulite development, the success of this regimen validates the plausibility of this concept. As such, this study has helped strengthen our understanding of cellulite formation and maintenance, which remains one of the most common aesthetic concerns of women worldwide. Based on this and on future research, it is certain that improved treatment modalities will continue to evolve.

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